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# Familial Transmission of a Deletion of Chromosome 21 Derived From a Translocation Between Chromosome 21 and an Inverted Chromosome 22

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**Chromosome analysis of a newborn boy with Down syndrome resulted in the identification of a family with an unusual derivative chromosome 22. The child has 46 chromosomes, including two chromosomes 21, one normal chromosome 22, and a derivative chromosome 22. Giemsa banding and fluorescent in situ hybridization (FISH) studies show that the derivative chromosome is chromosome 22 with evidence of both paracentric and pericentric inversions, joined to the long arm of chromosome 21 from 21q21.2 to qter. The rearrangement results in partial trisomy 21 extending from 21q21.2 to 21q terminus in the patient. The child's mother, brother, maternal aunt, and maternal grandmother are all carriers of the derivative chromosome. All have 45 chromosomes, with one normal chromosome 21, one normal chromosome 22, and the derivative chromosome 22. The rearrangement results in the absence of the short arm, the centromere, and the proximal long arm of chromosome 21 (del 21pter-21q21.2) in carriers. Carriers of the derivative chromosome in this family have normal physical appearance, mild learning disabilities and poor social adjustment. Am. J. Med. Genet. 70:399–403, 1997.** 

**KEY WORDS: chromosome 21; chromosome 22; chromosome inversion; translocation; familial rearrangement; Down syndrome**

## INTRODUCTION

Carriers of "pure" chromosome duplications and deletions are relatively uncommon. Individuals with deletions are often more severely affected than their trisomic counterparts. Few individuals are known to inherit their deletion, and few families with chromosomal deletions in multiple members are known to exist. Specifically, several cases of partial monosomies of 21q1 have been described [de Grouchy and Turleau, 1984]. However, most of these patients were later found to have unbalanced translocations, thereby resulting in monosomy and trisomy [Carpenter et al., 1986; Viljoen et al., 1992; Courtens et al., 1994]. Of the available reports, only five seem to describe "pure" deletions of bands q11.2-q21.2 on chromosome 21 [Fried et al., 1978; Modi and Buckton, 1982; Reynolds et al., 1985, Roland et al., 1990; Korenberg et al., 1991]. Only Roland et al. [1990] describe patients in whom the partially deleted chromosome 21 was inherited. According to these reports, the loss of the proximal long arm of chromosome 21 appears to be associated with mild mental deficit, but relatively few physical defects.

Structural chromosomal rearrangements may preferentially involve specific chromosomal segments. Chromosome 22 contains several unique repeated gene families [Emanuel et al., 1991]. Unequal crossing over between multiple members of these gene families could produce de novo deletions or other alterations of chromosome 22. Complex inversions with duplications and deletions involving this chromosome have been observed [Abeliovich et al., 1989; Driscoll et al., 1992; Prasher et al., 1995; Lindsay et al., 1995]. Deletions of 22q11.2 are associated with the DiGeorge anomaly and the velo-cardio-facial syndrome (VCFS) phenotype, including conotruncal cardiac malformations, cleft lip and palate, typical facial appearance, and psychiatric disorders [Scambler et al., 1991, 1992; Driscoll et al., 1992].

We report on a family with an unusual derivative chromosome 22 in several relatives, initially identified through a propositus with Down syndrome. The rearrangement proved to be more complex than could have been deduced by G-banding alone; multiple FISH stud-

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ies were necessary to solve the structure of the derivative chromosome. The chromosome consists of both paracentric and pericentric inversions of chromosome 22 joined to a deleted chromosome 21. The rearrangement results in a substantial deletion of chromosome 21 (21pter-21q21.2) in all carriers. The multiple breaks in chromosome 22 may also result in DNA loss or gene disruption at the breakage sites. The deletion of chromosome 21, possibly with a contribution from the inversions of chromosome 22, is associated with an apparently mild phenotype consisting of developmental delays, learning disabilities, and poor social adjustment in this family.

## MATERIALS AND METHODS

### Clinical Report

The propositus is a male infant born to a gr9p5 29-year-old mother. The child had classical Down syndrome. Birth weight was 2,840 g, length was 46 cm, and head circumference (OFC) was 33 cm, all at the 10th centile. At age 10 months the child weighed 7.1 kg (5th centile), length was 72 cm (25th centile), and OFC was 43 cm (5th centile). He also had mild alternating strabismus with hyperopia, slight astigmatism, and normal slit lamp and fundoscopic findings. Initial hearing screen results were normal. The palate and uvula were intact. Echocardiogram showed a small secundum atrial septal defect. Mild gastro-intestinal reflux subsided by age 10 months. There was generalized hypotonia and developmental delays. At 10 months he was not sitting without support. He had some babbling sounds and appeared to respond appropriately. An MRI has not been performed. Chest radiograph showed a normal thymic image and normal cardiac size. He is currently in foster care; the foster parents have applied for his adoption. His mother is a 29-year-old African-American woman, with a history of seizures, psychiatric problems, and learning disabilities. She attended special classes and left school at age 16 years. Of her nine pregnancies, four pregnancies were miscarried spontaneously. Of the five liveborn children, one died suddenly at 3 months. Her oldest child now has learning and behavior problems. The other two children are said to have developmental delays and are in foster care because of neglect and abuse. The maternal grandmother also attended special education classes.

Chromosome and FISH studies were performed on blood lymphocytes obtained from the boy, his mother, 7-year-old brother, 1-year-old brother, maternal aunt and her fetus, and the maternal grandmother. FISH studies with multiple probes were performed on the chromosome preparations of the patient's mother and aunt. Figure 1 depicts the pedigree of this family and shows the chromosome status of the relatives on whom studies were performed.

### Cytogenetic Analysis

Peripheral blood obtained on all relatives was prepared by standard cytogenetic methods to produce high resolution banding. Ethidium bromide was added to the cultures 2 hours before harvest to preserve chromosome length and enhance banding [Ikeuchi, 1984]. Metaphase cells were analyzed by G-banding, C-banding, and silver stain.

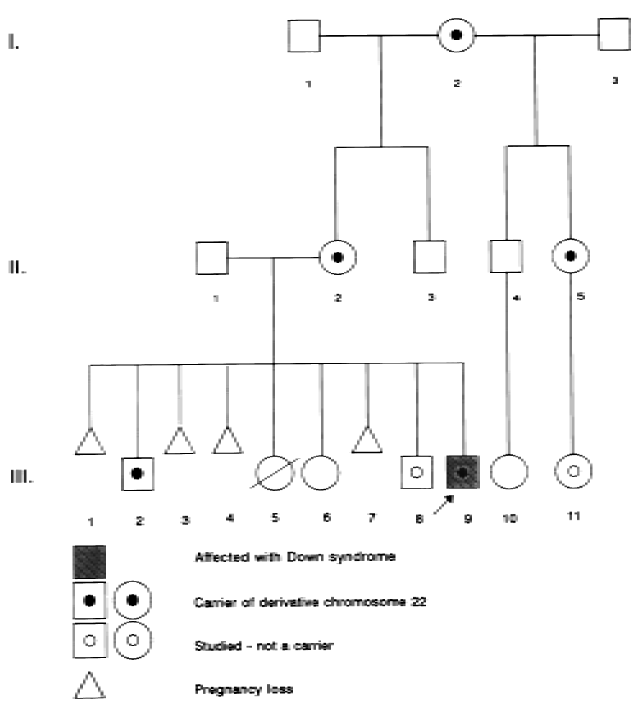


Fig. 1. Pedigree of the family.

### Fluorescent In Situ Hybridization (FISH)

FISH was performed with the following probes (ONCOR, Gaithersburg, MD): Biotin labelled alpha satellite probes specific to the pericentromeric region of chromosomes 13 and 21 (D13Z1/D21Z1); biotin labelled beta satellite DNA probes to all human acrocentric chromosomes; whole chromosome painting probes for chromosomes 21 and 22; a combination digoxigenin labeled cosmid DNA probe D22S75 (N25) specific to the DiGeorge region of chromosome 22 (22q11.21-q11.23), and a control probe D22S39; and the M-bcr (Major breakpoint) DNA probe, which hybridizes to a more distal region of 22q11. In addition, FISH was performed with probes from cosmids c11-60 and c443, cosmids from which two highly polymorphic short tandem repeat markers (D22S941 and D22S944) were developed. These markers are deleted in 82% of DiGeorge patients [Morrow et al., 1995] and are in the same general location as the D22S75 marker obtained from ONCOR.

## RESULTS

### Cytogenetic Analysis

An analysis of 20 cells from the propositus showed 46 chromosomes, with two normal chromosomes 21, one normal chromosome 22, and one derivative chromosome 22. C-banding demonstrated the derivative chromosome to be monocentric, and silver stain showed a secondary constriction in the middle of the short arm.

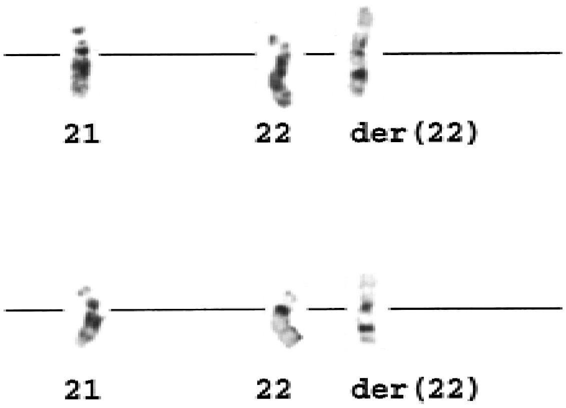


Fig. 2. Partial karyotype of chromosomes 21, 22, and the derivative chromosome 22 in the mother.

The newborn's mother, grandmother, aunt, and half brother all had 45 chromosomes: one normal chromosome 21, one normal chromosome 22, and one derivative chromosome 22. Figure 2 shows a partial G-banded karyotype of chromosomes 21 and 22, and Figure 3 shows a diagram of chromosomes 21, 22, and the proposed structure of the derivative chromosome 22 in association with DNA markers localized by FISH.

## FISH

The centromere of the derivative chromosome showed no hybridization with the alpha satellite probe D13Z1/D21Z1. Hybridization with beta satellite DNA localized beta satellite sequences in the proximal short arm. A coatosome 22 probe showed chromosome 22 sequences in the proximal long arm and the distal short arm. The coatosome 21 probe hybridized to the distal long arm. The combined cosmid probe for the DiGeorge region at 22q11.21 and control probe D22S39 (at 22q13.3) showed three signals on the derivative chromosome, instead of the expected two (Fig. 4). Hybridization with the cosmids c11-60 and c443, which probably flank the probe N25 (D22S75) [Morrow et al., 1995], showed that both were proximal to the breakpoint in the long arm where chromosome 21 is joined to chromosome 22. The probes were not duplicated, deleted, or inverted. Hybridization with the probe M-bcr also showed normal results. Thus, the chromosome must have undergone paracentric as well as pericentric inversions. Our interpretation of the rearrangement is der(22)t(21;22)(22qter-22q13.3::22q12.2-22q13.3: : 22p13-22q12.2::21q21.2-21qter).

## DISCUSSION

Reports of partial monosomies of 21q described in the literature can be divided into two general categories: 1) deletions that extend into band q22.1 and 2) deletions proximal to this band. Fried et al. [1978], Modi and Bucton [1982], and Reynolds et al. [1985] describe patients with similar de novo deletions of proximal 21q. Their patients had minor anomalies and mental retardation, but the clinical findings as described were not consistent. The deletions in these reports probably extend into band q22.1, and presumably account for the pronounced mental impairment. The report of Roland et al. [1990] describes a mother and daughter with an interstitial deletion of 21q11 to 21q21.3. Both patients had minor anomalies and mild mental retardation. Delay in fine and gross motor skills, language comprehension, and expressive language were noted in the daughter. Korenberg et al. [1991] describe deletion 21 q11.2-q21.2 in a male with normal intelligence, minor anomalies, and poor fine and gross motor skills. Thus, deletions not extending to 21 q22.1 seem to cause only minor anomalies and mild mental impairment. This is consistent with the observations of Gardiner et al. [1990] and Korenberg et al. [1994], in that the proximal part of chromosome 21 contains relatively few genes, while most critical chromosome 21 sequences localize to the distal half of the long arm. Similarly, our patient

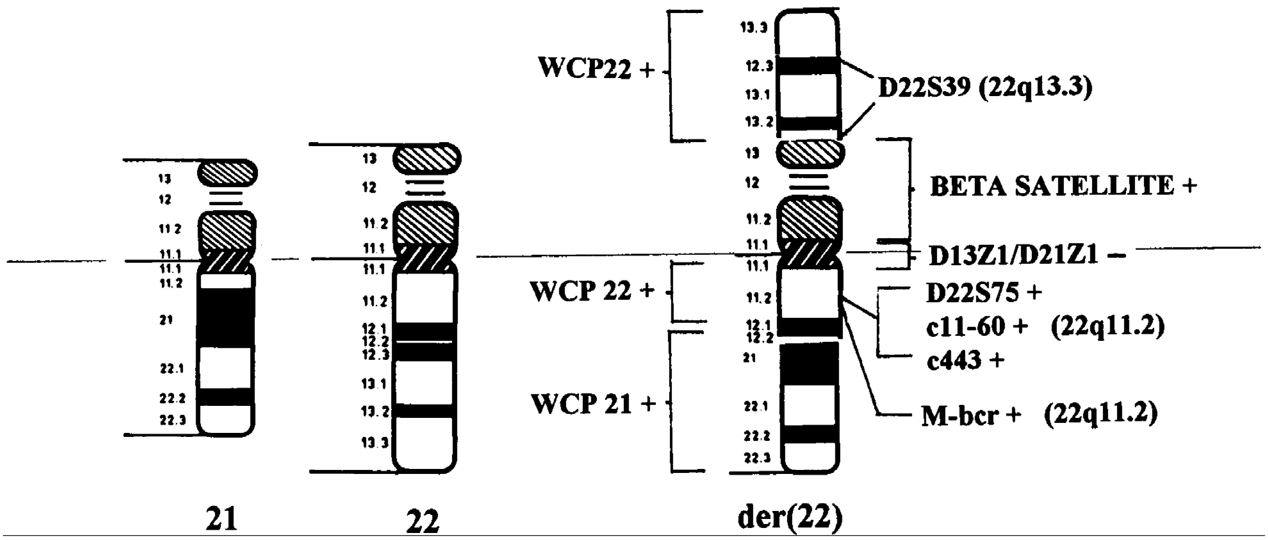


Fig. 3. Schematic representation of chromosomes 21, 22, and the proposed structure of the derivative chromosome 22. Whole chromosome paint (WCP) probes are depicted on the left of the derivative chromosome, and the FISH probes utilized to solve its structure are on the right.

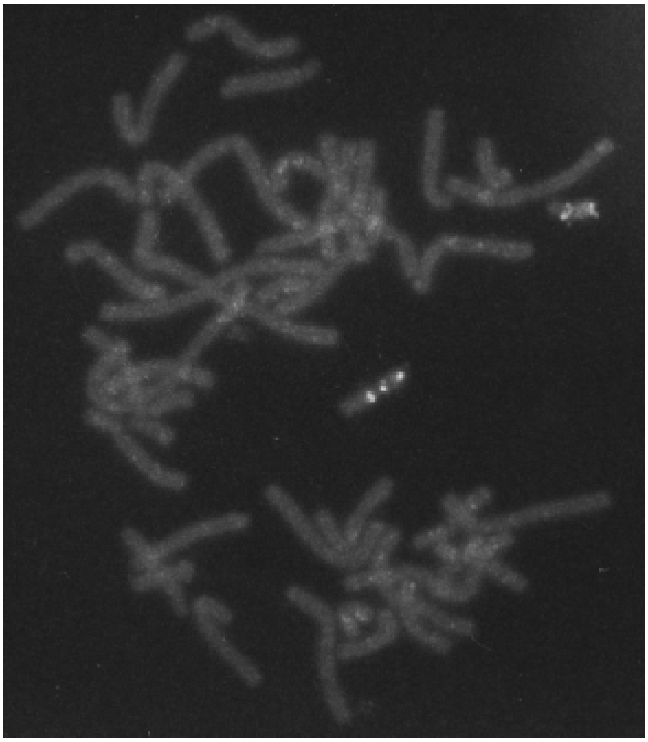

Fig. 4. Fluorescent in situ hybridization with probe D22S25 and control probe D22S39. Note two signals on the normal chromosome 22 and three signals on the derivative chromosome 22.

with Down syndrome did not have complete trisomy 21 but was trisomic only for the part of chromosome 21 not deleted in his relatives. Patients with duplications of the very small proximal 21q region show no signs of Down syndrome but usually have short stature, microcephaly, and mental retardation [Park, 1987; Korenberg at al., 1994].

Carriers of reciprocal translocations or derivative chromosomes are at increased risk for producing gametes with unbalanced chromosome complements [Stene and Stengel-Rutkowski, 1988]. The risk for a liveborn child with a chromosome abnormality is especially high when one of the chromosomes involved in the translocation is a 21, as adjacent segregation during meiosis may lead to functional trisomy 21 in the offspring. Due to the birth of a child with Down syndrome, we identified 4 individuals spanning 3 generations in a single family with deletion 21pter to 21q21. Deletion carriers had no anomalies but "poor" social adjustment, behavior problems and learning difficulties. However, it is difficult to distinguish the contribution of this chromosomal defect from other environmental and psychological factors operating in this family.

The derivative chromosome also exhibited three signals with the D22S75/D22S39 probe combination. In order to investigate the inversion breakpoints, we performed FISH with cosmids in the same general area as D22S75. These cosmids showed normal hybridization signals, suggesting that the break must have occurred in the D22S39 region. This presupposes a more complex rearrangement of chromosome 22 than could be deduced from G-banding. However, it appears that chromosome 22 is not deleted, although a minute loss of DNA in the breakpoint regions cannot be ruled out. It is unlikely that a duplication exists in the 22q13.3 region, as carriers of such duplications have anomalies including coloboma of the iris, Pierre Robin anomaly, generalized muscle hypertonia, delayed psychomotor development, and, later, mental retardation. [Abeliovich et al., 1989; Prasher et al., 1995]. Deletion of 22q11.2 is associated with the DiGeorge/VCFS phenotype [Scrambler et al., 1991, 1992; Driscoll et al., 1992]. The DiGeorge/VCFS manifestations consist of multiple anomalies, including cleft palate, heart malformations, facial characteristics, and learning disabilities [Shprintzen, 1978; reviewed by Goldberg et al., 1993]. Preliminary studies on our patient showed normal thymic function, although he had a small atrial septal defect of the secundum type. His face, palate and, uvula did not suggest the VCFS.

In conclusion, we describe a family in which a derivative chromosome 22 was identified. The chromosome was transmitted through the female line in three generations. The carriers are monosomic for the proximal short arm of chromosome 21 and have a complex inversion of chromosome 22. The relatives did not have findings of the VCFS but had mild learning disabilities and poor social adjustment, further confirming that "pure" deletions of chromosome 21, which do not extend into band 21q22.1, result only in a mild phenotype. The rearrangement of chromosome 22 illustrates that contrary to observations based on classical banding techniques, very complex rearrangements, consisting of multiple breaks, are possible. It remains to be elucidated if certain chromosomes or chromosome regions are more prone to such rearrangements and to determine the predisposing factors and mechanisms for such rearrangements.

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